GB2140687

Title:
Osmotic drug delivery system

Abstract:

An osmotic system is disclosed comprising a wall 12, 23 formed in at least a part of a semipermeable material that surrounds a compartment 14. The compartment contains a first osmotic composition 15, 16, 17 comprising a beneficial agent 15, and a second and different osmotic composition 18, 19. A passageway 13 in the wall connects the first composition with the exterior of the system.

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(51) INT CL³
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(52) Domestic classification
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(56) Documents cited

GB A	2116842	EP A2	0040899
GB	1551898	EP A1	0010876
GB	1511614	US	4327725
GB	1385521	US	4111202

(58) Field of search
A5B

(54) Osmotic drug delivery system

(57) An osmotic system is disclosed comprising a wall 12, 23 formed in at least a part of a semipermeable material that surrounds a compartment 14. The compartment contains a first osmotic composition 15, 16, 17 comprising a beneficial agent 15, and a second and different osmotic composition 18, 19. A passageway 13 in the wall connects the first composition with the exterior of the system.

FIG. 2

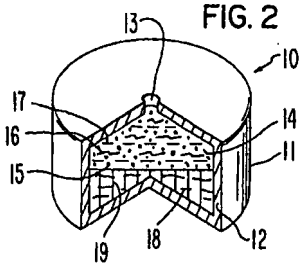
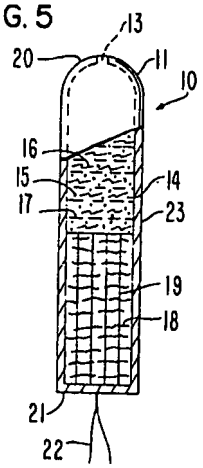


FIG. 5



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This print takes account of replacement documents submitted after the date of filing to enable the application to comply with the formal requirements of the Patents Rules 1982.

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FIG. 1

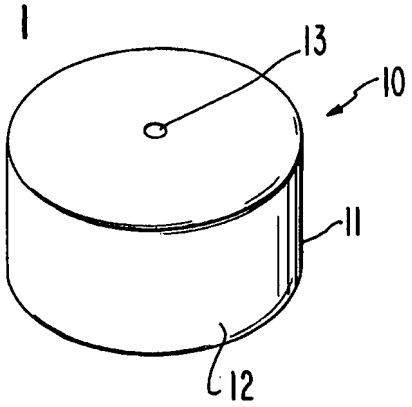

FIG. 2

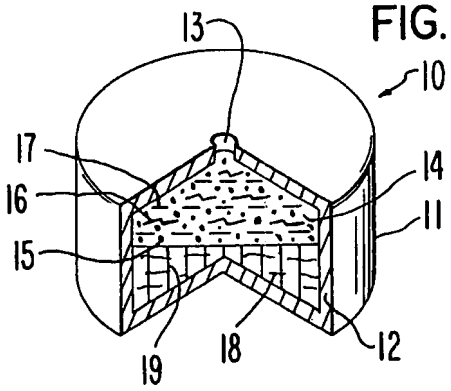

FIG. 3

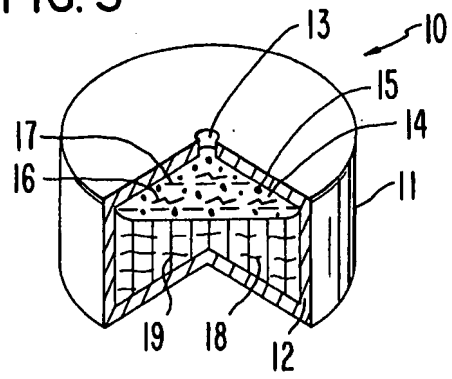

FIG. 4

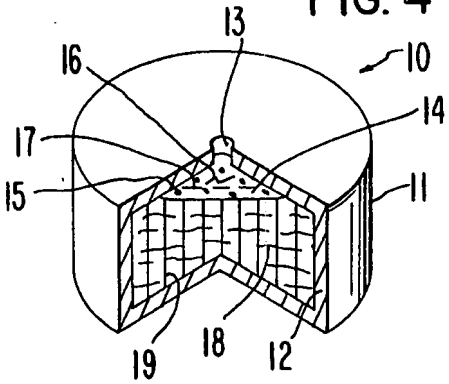

FIG. 5

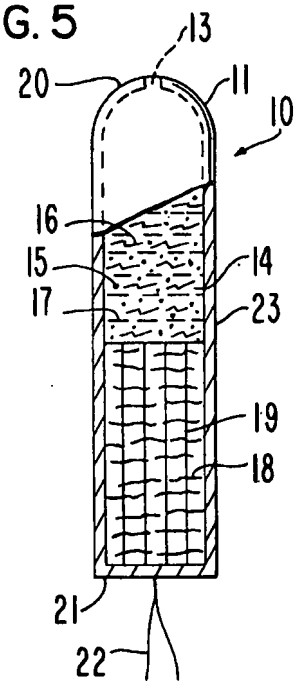

FIG. 6

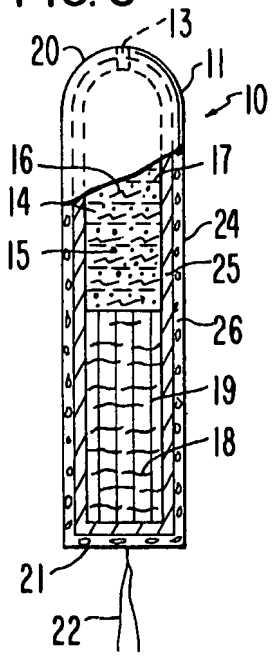

FIG. 7

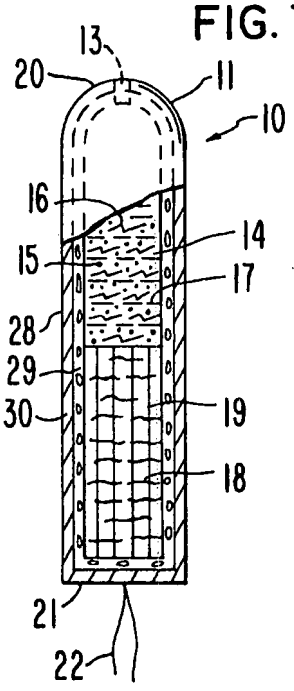

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FIG. 8

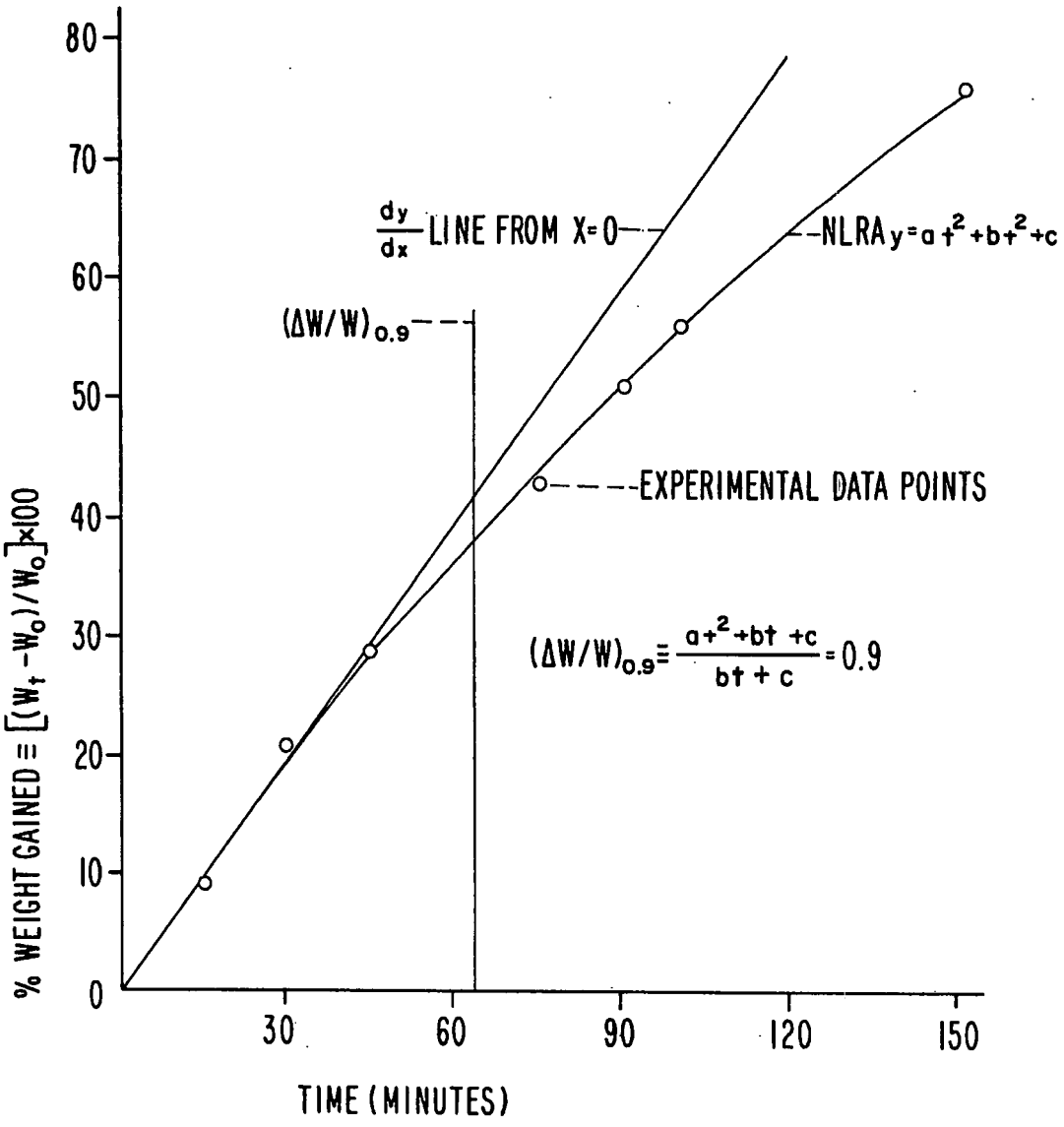

FIG. 9

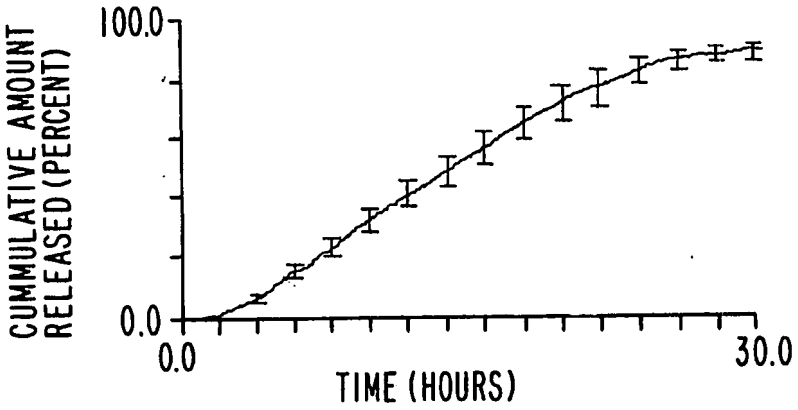

FIG. 10

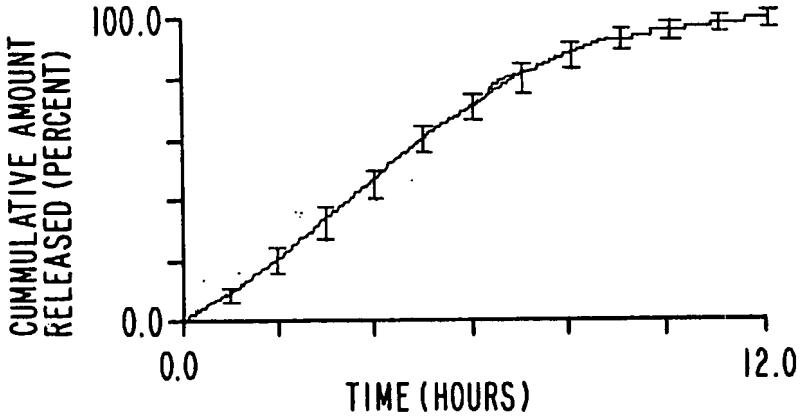

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FIG. II

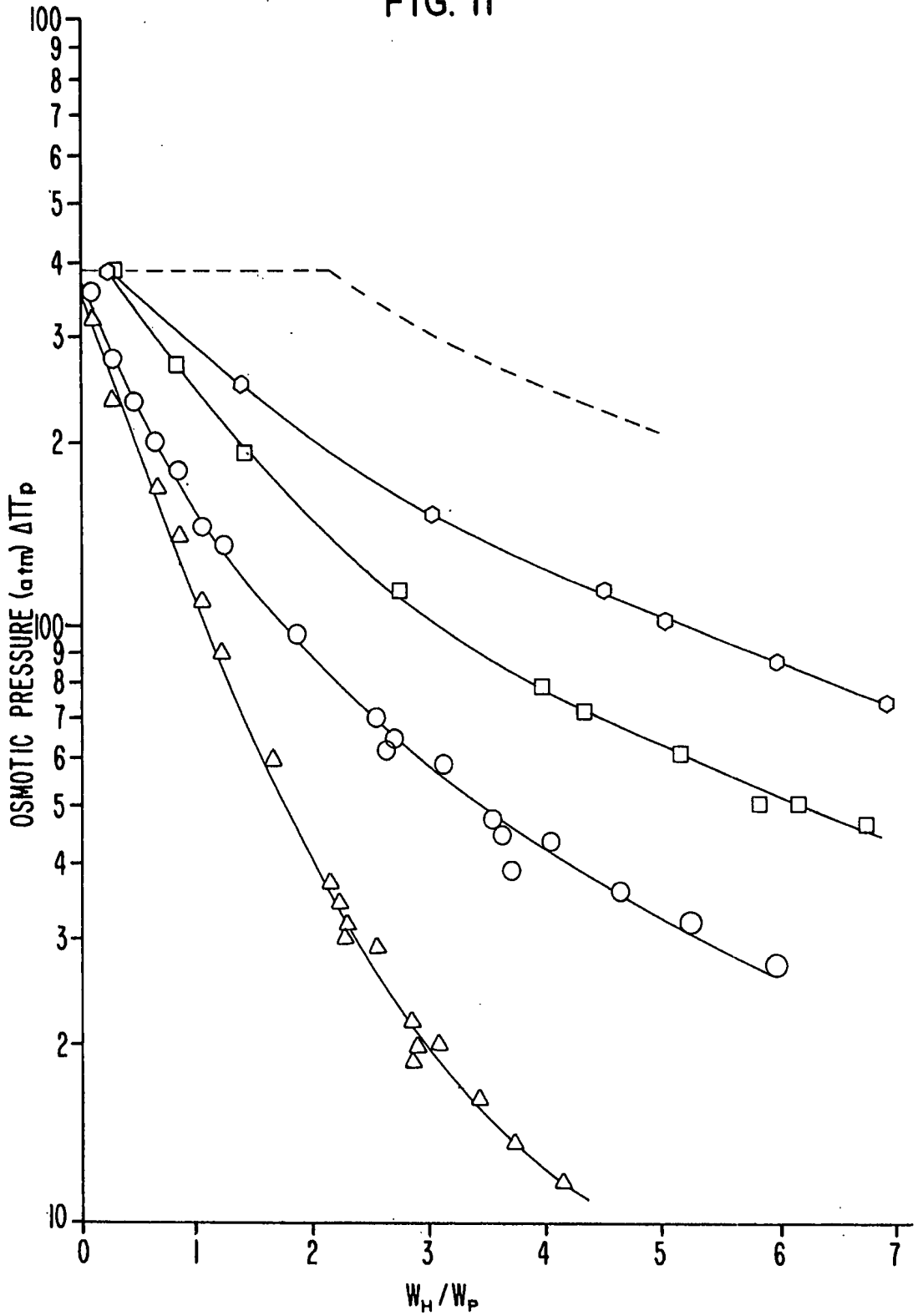


FIG. 12

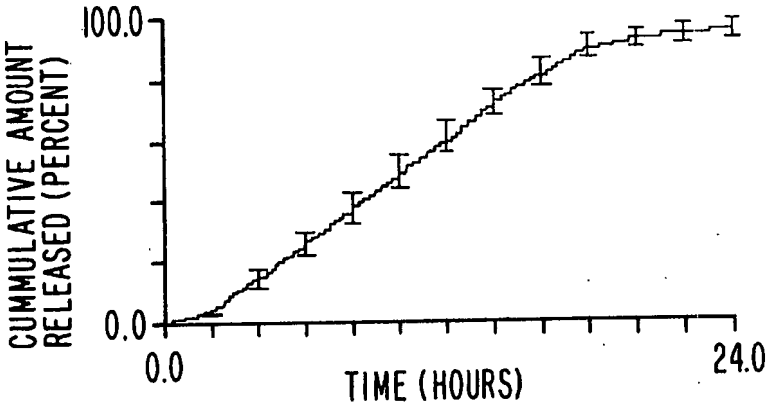


FIG. 13

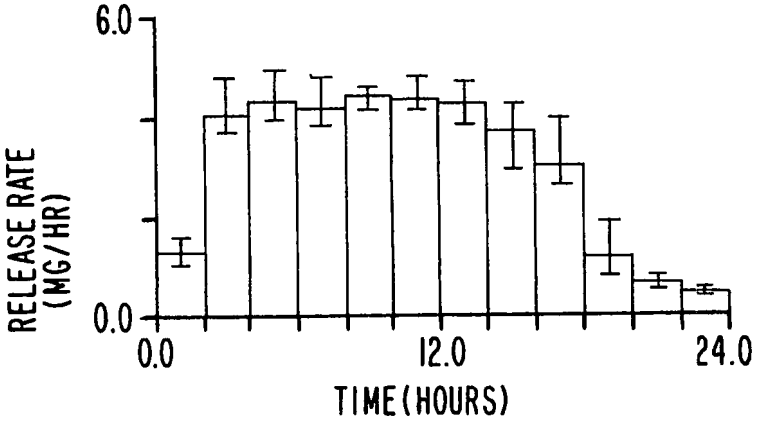


FIG. 14

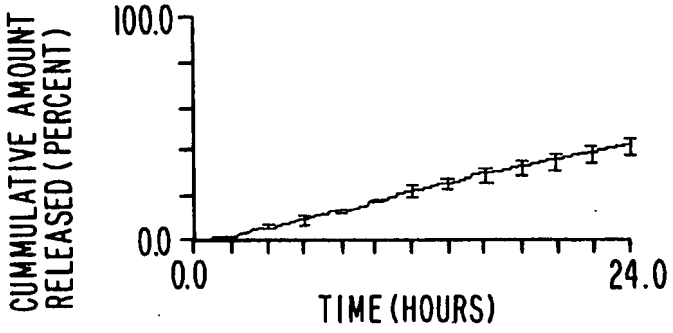


FIG. 15

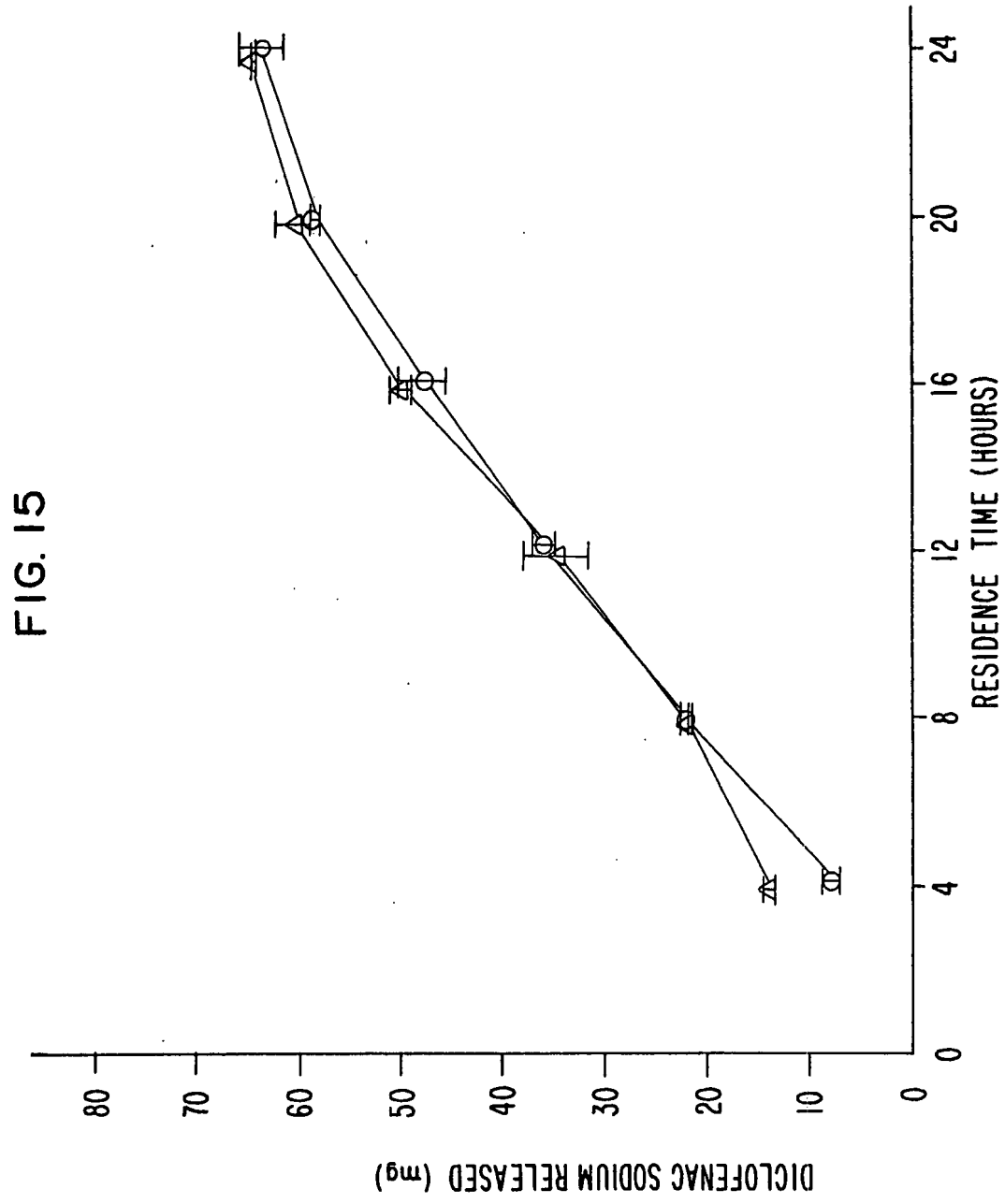
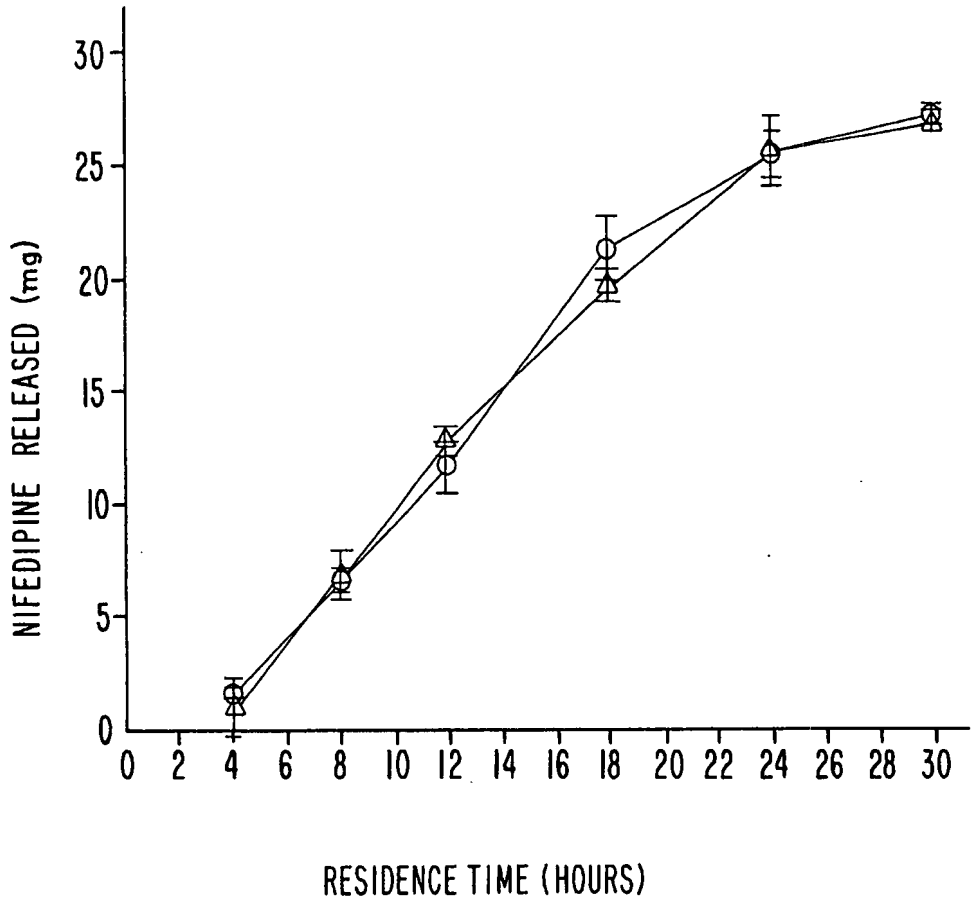


FIG. 16



SPECIFICATION

Osmotic Device With Dual Thermodynamic Activity

This invention pertains to both a novel and unique delivery system. More particularly, the invention relates to an osmotic device comprising a wall formed in at least a part of a semi-permeable material that surrounds a compartment comprising: (1) a first osmotic composition comprising a beneficial agent, and preferably an osmagent and/or an osmopolyer, said composition in contacting arrangement with (2) a second osmotic composition comprising an osmagent and an osmopolymer. A passageway through the wall connects the exterior of the osmotic device with the first osmotic composition containing the beneficial agent for delivering the first composition from the osmotic device. The osmotic device is useful for delivering beneficial agents that because of their solubilities are difficult to deliver in a known amount at a controlled rate from an osmotic dispensing system.

Background of the Invention

Since the beginning of antiquity, both pharmacy and medicine have sought a delivery system for administering a beneficial drug. The first written reference to a dosage form is in the Eber Papyrus, written about 1552 B.C. The Eber Papyrus mentions dosage forms such as anal suppositories, vaginal pessaries, ointments, oral pill formulations, and other dosage preparations. About 2500 years passed without any advance in dosage form development, when the Arab physician Rhazes, 865—925 A.D., invented the coated pill. About a century later the Persian Avicenna, 980—1037 A.D., coated pills with gold or silver for increasing patient acceptability and for enhancing the effectiveness of the drug. Also around this time, the first tablet was described in Arabian manuscrips written by al-Zahrawi, 936—1009 A.D. The manuscrips described a tablet formed from the hollow impressions in two facing tablet molds. Pharmacy and medicine waited about 800 years for the next innovation in dosage forms, when in 1883 Mothes invented the capsule for administering drug. The next quantum leap in dosage forms came in 1972 with the invention of the osmotic delivery device by inventors Theeuwes and Higuchi as disclosed in United States Pat. Nos. 3,845,770 and 3,916,899. The osmotic devices disclosed in those patents comprise a semi-permeable wall that surrounds a compartment containing a useful agent. The wall is permeable to the passage of an external fluid, and it is substantially impermeable to the passage of useful agent. There is a passageway through the wall for delivering the useful agent from the osmotic device. These devices release useful agent by fluid being imbibed through the semi-permeable wall into the compartment at a rate determined by the permeability of the semi-permeable wall and the osmotic pressure gradient across the semi-permeable wall to produce an aqueous solution containing useful agent that is dispensed through the passageway from the device. These devices are extraordinarily effective for delivering a useful agent that is soluble in the fluid and exhibits an osmotic pressure gradient across the semi-permeable wall against the external fluid.

A pioneer advancement in osmotic delivery devices was presented to the dispensing arts by inventor Felix Theeuwes In United States Patent No. 4,111,202. In this patent, the delivery kinetics of the osmotic device is enhanced for delivering useful agents that are insoluble to very soluble in the fluid, by manufacturing the osmotic device with a useful agent compartment and an osmagent compartment separated by a film. The film is movable from a rested to an expanded state. The osmotic device delivers agent by fluid being imbibed through the semi-permeable wall into the osmagent compartment producing a solution that causes the compartment to increase in volume and act as a driving force that is applied against the film. This force urges the film to expand against the useful agent compartment and correspondingly diminish the volume of the useful agent compartment, whereby useful agent is dispensed through the passageway from the osmotic device. While this device operates successfully for its intended use, and while it can deliver numerous useful agents of varying solubilities, Its use can be limited because of the manufacturing steps and costs needed for fabricating and placing the movable film in the compartment of the osmotic device.

In United States Patent No. 4,327,725 patentees Richard Cortese and Felix Theeuwes provided an osmotic dispensing device for delivering beneficial agents, that because of their solubilities in aqueous and biological fluids, are difficult to deliver in meaningful amounts at controlled rates over time. The osmotic devices of this patent comprise a semi-permeable wall surrounding a compartment containing a beneficial agent that is insoluble to very soluble in aqueous and biological fluids, and an expandable hydrogel. In operation the hydrogel expands in the presence of external fluid that enters the device thereby causing the beneficial agent to be dispensed through the passageway from the device. This device operates successfully for its intended use, and it delivers many difficult to deliver beneficial agents for their intended purpose. Now it has been observed, its use can be limited because the hydrogel lacks a present ability to imbibe sufficient fluid for the maximum self-expansion needed for urging the beneficial agent from the device.

It will be appreciated by those versed in the dispensing art, that if an osmotic device can be provided that exhibits a high level of osmotic activity for delivering a beneficial agent by generating in situ an expanding force sufficient for delivering the maximum amount of agent at a controlled rate from an osmotic device, such an osmotic device would have a positive value and represent an advancement in the dispensing art. Likewise, it will be immediately appreciated by those versed in the dispensing art

that if an osmotic device is made available possessing dual thermodynamic osmotic activity for delivering increased amounts of a beneficial agent, said osmotic device would find practical application in the fields of pharmacy and medicine.

Object of the Invention

Accordingly, in view of the above presentation, it is an immediate object of this invention to provide an osmotic system that represents a further improvement and advancement in the dispensing art.

Another object of the invention is to provide an osmotic system manufactured in the form of an osmotic device for delivering in vivo a beneficial drug that is difficult to deliver and now can be delivered by the osmotic device provided by this invention in therapeutically effective amounts over time.

Another object of the invention is to provide an osmotic system possessing dual osmotic activity, which system comprises a compartment containing a first osmotic composition comprising a drug, and preferably an osmagent and/or an osmopolymer, and a second osmotic composition comprising an osmagent and an osmopolymer, with the compositions acting in concert for delivering the drug from the osmotic device.

Yet another object of the invention is to provide an osmotic device having means for high loading of a water-insoluble or a slightly water-soluble drug and means for delivering the drug in either instance at a controlled rate and continuously over time.

Yet another object of the invention is to provide an osmotic device that can deliver a pH dependent beneficial agent by providing a neutral medium for delivering the beneficial agent in a finely dispersed form for increasing its surface area and for maximizing the dissolution rate of the beneficial agent.

Still yet another object of the invention is to provide an osmotic system for delivering a drug having a very low dissolution rate that is the rate-limiting step for delivering the drug from the system, but now can be delivered by using an osmotic composition that functions in situ as a wetting agent and a solubilizing agent for increasing the dissolution rate and the solubility of the drug, thereby enhancing its delivery from the osmotic system.

Still yet another object of the invention is to provide an osmotic system comprising means for maintaining a high level of osmotic activity of a polymer used for delivering a beneficial agent from the osmotic system.

Still a further object of the invention is to provide an osmotic, therapeutic device that can administer a complete pharmaceutical dosage regimen comprising poorly soluble to very soluble agents, at a controlled rate and continuously, for a particular time period, the use of which requires intervention only for the initiation and possible termination of the regimen.

Other objects, features, aspects and advantages of the invention will be more apparent to those versed in the dispensing art from the following detailed specification taken in conjunction with the figures and the accompanying claims.

Brief Description of the Drawings

In the drawings, which are not drawn to scale, but are set forth to illustrate various embodiments of the invention, the drawing figures are as follows:

Figure 1 is an isometric view of an osmotic device designed for orally administering a beneficial agent to the gastrointestinal tract;

Figure 2 is an opened view of the osmotic device of Figure 1 illustrating the structure of the osmotic device of Figure 1;

Figure 3 is an opened view of the osmotic device of Figure 1 illustrating the osmotic device in operation and delivering a beneficial agent from the osmotic device;

Figure 4 is an opened view of the osmotic device of Figure 1 considered with Figure 3 illustrating the osmotic device in operation and delivering a major amount of a beneficial agent from the osmotic device;

Figure 5 shows an osmotic therapeutic device with its wall partially broken away, designed for delivering a beneficial agent into a body passageway, such as the ano-rectal and vaginal passageways;

Figure 6 shows the osmotic device of Figure 5 with a different wall structure;

Figure 7 shows the osmotic device of Figure 5 depicting a different wall structure than the wall structure depicted in Figure 6.

Figure 8 represents the weight gain as a function of time for a polymer encapsulated in a semi-permeable membrane when the encapsulated polymer is placed in water;

Figure 9 depicts the cumulative amount of drug released from a device comprising an osmopolymer having two different molecular weights;

Figure 10 depicts the cumulative amount of drug released from a device using a different set of osmopolymers;

Figure 11 depicts the osmotic pressure curves for a number of osmagent and a number of osmopolymer/osmagent compositions;

Figure 12 depicts the cumulative release profile for an osmotic system using two different osmopolymers;

Figure 13 depicts the release rate per hour for an osmotic system different from Figure 9 containing an osmopolymer having two different molecular weights;

Figure 14 depicts the cumulative amount released from a single composition device comprising only one layer;

Figure 15 illustrates the in vivo and in vitro cumulative release for one drug delivered by the osmotic device;

Figure 16 illustrates the in vivo and in vitro cumulative release for a different drug delivered by an osmotic device.

In the drawings and the specification, like parts in related figures are identified by like parts. The terms appearing earlier in the specification and in the description of the drawings, as well as embodiments thereof, are further detailed elsewhere in the disclosure.

Detailed Description of the Drawings

Turning now to the drawings in detail, which are examples of various osmotic devices provided by the invention, and which examples are not to be construed as limiting, one example of an osmotic device is seen in Figure 1. In Figure 1, osmotic device 10 is seen comprising a body member 11 having a wall 12 and a passageway 13 for releasing a beneficial agent from osmotic device 10.

In Figure 2, osmotic device 10 of Figure 1 is seen in opened section. In Figure 2, osmotic device 10 comprises a body 11, a semipermeable wall 12 that surrounds and forms internal compartment 14, that communicates through a passageway 13 with the exterior of osmotic device 10. Compartment 14 contains a first osmotic composition comprising a beneficial agent 15, represented by dots, and it can be from insoluble to very soluble in fluid imbibed into compartment 14, an osmagent 16, represented by wavy lines, that is soluble in fluid imbibed into compartment 14 and exhibits an osmotic pressure gradient across semi-permeable wall 12 against an external fluid, and, an osmopolymer 17, represented by horizontal dashes, that imbibes fluid into compartment 14 and exhibits an osmotic pressure gradient across semi-permeable wall 12 against an exterior fluid present in the environment of use. Wall 12 is formed of a semi-permeable composition that is substantially permeable to the passage of the exterior fluid, and it is substantially impermeable to the passage of the exterior fluid, and it is substantially impermeable to the passage of agent 15, osmagent 16 and osmopolymer 17. Semi-permeable wall 12 is non-toxic and it maintains its physical and chemical integrity during the delivery life of device 10.

Compartment 14 also houses a second osmotic composition that is distant from passageway 13 and in contacting relation with the first composition. The second composition is an expandable driving force that acts in co-operation with the first osmotic composition for delivering the maximum amount of beneficial agent 15 from osmotic device 10. The second osmotic composition comprises an osmagent 18, that is soluble in fluid imbibed into compartment 14 and exhibits an osmotic pressure gradient across wall 12 against an external fluid, blended with an osmopolymer 19 that imbibes fluid into compartment 14 and exhibits an osmotic pressure gradient across wall 12 against external fluid. Osmopolymers 17 and 19 are hydrophilic water soluble or lightly cross-linked water insoluble polymers, and they possess osmotic properties such as the ability to imbibe external fluid, exhibit an osmotic pressure gradient across the semipermeable wall against the external fluid, and swell or expand in the presence of the fluid. Osmopolymers 17 and 19 are mixed with osmagent 16 and 18 for imbibing the maximum volume of external fluid into compartment 14. This fluid is available to osmopolymers 17 and 19 to optimize the volumetric rate and for total expansion of osmopolymers 17 and 19. That is, osmopolymers 17 and 19 absorb fluid imbibed into compartment 14 by the osmotic imbibition action of osmopolymers 17 and 19 supplemented by the osmotic imbibition action of osmagents 16 and 18 for effecting the maximum expansion of osmopolymers 17 and 19 to an enlarged state.

In operation, the delivery of beneficial agent 15 from osmotic device 10 is carried out, in one presently preferred embodiment, by (1) imbibition of fluid by the first composition to form a suspension in situ and delivery of the suspension through the passageway; and concurrently by (2) imbibition of fluid by the second composition causing the second composition to swell and co-operate with the first composition for driving the agent suspension through the passageway. According to the operation described, the osmotic device may be treated as a cylinder, with the second composition expanding like the movement of a piston for aiding in delivering the agent suspension from the osmotic device. Although the shape of the osmotic device as depicted in Figs. 1 and 2 is not a true cylinder, it is approximate enough for the following physical analysis. In this analysis, the volume rate delivered by the osmotic device F_t is composed of two sources; the water imbibition rate by the first composition F, and the water imbibition rate by the second composition Q wherein:

$$F_t = F + Q \qquad (1)$$

Since the boundary between the first composition and the second composition hydrates very

little during the functioning of the osmotic device, there is insignificant water migration between the compositions. Thus, the water imbibition rate of the second composition, Q, equals the expansion of its volume,

$$\frac{dv_p}{dt}=Q \quad (2)$$

The total delivery rate from the osmotic device is then,

$$\frac{dm}{dt}=F_t \cdot C=(F+Q)C \quad (3)$$

wherein C is the concentration of beneficial agent in the delivered slurry. Conservation of the osmotic device volume, V, and the surface area, A, gives equation 4 and 5:

$$V=V_d+V_p \quad (4)$$

$$A=A_d+V_p \quad (5)$$

wherein V_d and V_p equal the volumes of the first composition and the second composition respectively; and wherein A_d and A_p equal the surface area contact with the wall by the first composition and the second composition respectively. In operation, both V_p and A_p increase with time while V_d and A_d decrease with time as the device delivers beneficial agent.

The volume of the second composition that expands with time when fluid is imbibed into the compartment is given by equation 7:

$$V_p=\int\left(\frac{W_H}{W_p}\right) \quad (7)$$

wherein, W_H is the weight of fluid imbibed by the second composition, W_p is the weight of the second composition initially present in the device, W_H/W_p is the ratio of fluid to initial solid of the second composition, V_p equals

$$\left(1+\frac{W_H}{W_p}\right)\frac{W_p}{e}$$

wherein e is the density of the second composition corresponding to W_H/W_p. Thus, based on the geometry of a cylinder, where r is radius of the cylinder, the area of imbibition is related to the volume of the swollen second composition as follows:

$$A_p=r^2+\frac{2\,W_p}{r\ e}\left(1+\frac{W_H}{W_p}\right) \quad (8)$$

$$A_d=A-A_p \quad (9)$$

The fluid imbibition rates into each compartment are:

$$F=\left(\frac{k}{h}\right)(A_d\,\Delta\pi_d) \quad (10)$$

$$Q=\left(\frac{k}{h}\right)(A_p\,\Delta\pi_p) \quad (11)$$

wherein k equals the osmotic permeability of the wall, h equals the wall thickness, $\Delta\pi_d$ and $\Delta\pi_p$ are the osmotic gradients for the first composition and the second composition respectively.

The total delivery rate, therefore, is:

$$\frac{dm}{dt} = \frac{k}{h} C A - \pi r^2 - \frac{2}{Y}\frac{W_p}{p} 1 + \frac{W_H}{W_p} \Delta\pi d + \pi p^2 + \frac{2}{r}\frac{W_p}{p} 1 + \frac{W_H}{W_p} \Delta\pi p \quad (12)$$

Figures 3 and 4 illustrate the osmotic device in operation as described for Figures 1 and 2. In Figures 3 and 4, for osmotic device 10, fluid is imbibed by the first composition at a rate determined by the permeability of the wall and the osmotic pressure gradient across the wall. The imbibed fluid continuously forms a solution containing beneficial agent, or a solution or of gel osmagent and osmopolymer containing beneficial agent in suspension, which solution or suspension in either operation is released by the combined operations of device 10. These operations include the solution, or the suspension being osmotically delivered through the passageway due to the continuous formation of solution or suspension, and by the swelling and increasing volume of the second composition, represented by the increase in height of the vertical lines in Figure 3 and 4. This latter swelling and increase in volume applies pressure against the solution or suspension thereby aiding the first composition and simultaneously causing delivery of beneficial agent to the exterior of the device.

The first composition and the second composition act together to substantially insure that delivery of beneficial agent from the compartment is constant over a prolonged period of time by two methods. *First,* the first composition imbibes external fluid across the wall, thereby forming either a solution or a suspension, the latter fraction of which would be substantially delivered at non-zero order (without the second composition present), since the driving force decays with time. *Second, the second composition* operates by two simultaneous operations: first, the second composition operates to continuously concentrate beneficial agent by imbibing some fluid from the first composition to help keep the concentration of beneficial agent from falling below saturation, and second, the second composition by imbibing external fluid across the wall continuously increases in volume; thereby exerting a force against the first composition and diminishing the volume of beneficial agent, thusly directing beneficial agent to the passageway in the compartment. Additionally, since the extra solution or suspension formed in the first comparment is squeezed out, the osmotic composition cosely contacts the internal wall and generates a constant osmotic pressure, and therefore a constant delivery rate, in conjunction with the second composition. The swelling and expansion of the second composition, with its accompanying increase in volume, along with the simultaneous corresponding reduction in volume of the first composition, assures the delivery of beneficial agent at a controlled rate over time.

Device 10 of Figures 1 through 4 can be made into many embodiments including the presently preferred embodiments for oral use, for releasing either a locally or systemically acting therapeutic agent in a gastrointestinal tract. Oral system 10 can have various conventional shapes and sizes such as round with a diameter or 3/16 inches to 1/2 inch. In these forms, system 10 can be adapted for administering beneficial agent to numerous animals, including warm-blooded animals, humans, avains, reptiles and pisces.

Figures 5, 6 and 7 show another embodiment, an osmotic device 10 designed for placement in a body passageway, such as a vagina, or the ano-rectal canal. Device 10 has an elongated, cylindrical, self-sustaining shape with a rounded lead end 20, a trailing end 21, and it is equipped with manually controlled strings 22 for easily removing device 10 from a biological passageway. Device 10 is structurally identical with device 10 as described above and it operates in a like manner. In Figure 5, device 10 is depicted with a semi-permeable wall 23, in Figure 6 with a laminated wall 24 comprising an inner semi-permeable lamina 25 adjacent to compartment 14, and an external microporous lamina 26 distant from compartment 14. In Figure 7, device 10 comprises a laminated wall 28 formed of a microporous lamina 29 next to compartment 14, and a semi-permeable lamina 30 facing the environment of use and in laminar arrangement with microporous lamina 29. Device 10 delivers a beneficial agent for absorption by the vaginal mucosa, or the ano-rectal mucosa, to produce an in vivo local or systemic effect over a prolonged period of time.

The osmotic devices of Figures 1 through 7 can be used for delivering numerous agents including drugs at a controlled rate independent of the drug pH-dependency, or where the dissolution rate of the agent can vary between low and high in fluid environments, such as gastric fluid and intestinal fluid. The osmotic devices also provide for the high loading of agents of low solubility and their delivery at meaningful, therapeutic amounts. And, while Figures 1 through 7 are illustrative of various osmotic devices that can be made according to the invention, it is to be understood these devices are not to be construed as limiting, as the devices can take a wide variety of shapes, sizes and forms for delivering beneficial agents to the environment of use. For example, the devices include buccal, implant, artifical gland, cervical intrauterine, ear, nose, dermal, subcutaneous and blood delivery devices. The devices also can be sized, shaped, structured and adapted for delivering an active agent in streams, aquariums, field, factories, reservoirs, laboratory facilities, hot houses, transportation means, naval means, military means, hospitals, veterinary clinics, nursing homes, farms, zoos, sickrooms, chemical reactions, and other environments of use.

Detailed Description of the Invention

In accordance with the practice of this invention, it has now been found that osmotic delivery device 10 can be manufactured with a first osmotic composition and a second osmotic composition mutually housed in co-operative relationship in the compartment of the device. The compartment is formed by a wall comprising a material that does not adversely affect the beneficial agent, osmagent, osmopolymer and the like. The wall is permeable to the passage of an external fluid such as water and biological fluids, and it is substantially impermeable to the passage of agents, osmagents, osmopolymers, and the like. The wall is formed of a material that does not adversely affect an animal or a host, and the selectively semi-permeable materials used for forming the wall are non-erodible and they are insoluble in fluids. Typical materials for forming the wall are in one embodiment cellulose esters, cellulose ethers and cellulose ester-ethers. These cellulosic polymers have a degree of substitution, D.S., on the anhydroglucose unit, from greater than 0 up to 3 inclusive. By degree of substitution is meant the average number of hydroxyl groups originally present on the anhydroglucose unit comprising the cellulose polymer that are replaced by a substituting group. Representative materials include a member selected from the group consisting of cellulose acylate, cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose diacetate, cellulose triacetate, mono, di and tricellulose alkanylates, mono, di and tricellulose aroylates, and the like. Exemplary polymers include cellulose acetate having a D.S. up to 1 and an acetyl content up to 21%; cellulose acetate having an acetyl content of 32 to 39.8; cellulose acetate having a D.S. of 1 to 2 and an acetyl content of 21 to 35%; cellulose acetate having a D.S. of 2 to 3 and an acetyl content of 35 to 44.8%; and the like. More specific cellulosic polymers include cellulose propionate having a D.S. of 1.8 and a propionyl content of 39.2 to 45% and a hydroxyl content of 2.8 to 5.4%; cellulose acetate butyrate having a D.S. of 1.8, an acetyl content of 13 to 15% and a butyryl content of 34 to 39%; cellulose acetate butyrate having an acetyl content of 2 to 29%, a butyryl content of 17 to 53% and a hydroxyl content of 0.5 to 4.7%; cellulose triacylates having a D.S. of 2.9 to 3 such as cellulose trivalerate, cellulose trilaurate, cellulose tripalmitate, cellulose trisuccinate, and cellulose trioclanoate; cellulose diacylates having a D.S. of 2.2 to 2.6 such as cellulose disuccinate, cellulose dipalmitate, cellulose dioclanoate, cellulose dipentale, coesters of cellulose such as cellulose acetate butyrate and cellulose acetate propionate, and the like.

Additional semi-permeable polymers include ethyl cellulose, cellulose nitrate, acetaldehyde dimethyl acetate, cellulose acetate ethyl carbamate, cellulose acetate methyl carbamate, cellulose acetate dimethyl aminoacetate, semi-permeable polyamides, semi-permeable polyurethanes, semi-permeable sulfonated polystyrenes, cross-linked selectively semi-permeable polymers formed by the coprecipitation of a polyanion and a polycation as disclosed in U.S. Pat. Nos. 3,173,876; 3,276,586; 3,541,005; 3,541,006; and 3,546,142; semi-permeable polymers as disclosed by Loeb and Sourirajan in U.S. Pat. No. 3,133,132; lightly cross-linked polystyrene derivatives; cross-linked poly(sodium styrene sulfonate), cross-linked poly(vinylbenzyltrimethyl amonium chloride), semi-permeable polymers exhibiting a fluid permeability of 10^{-5} to 10^{-1} (cc.mil/cm^2.hr.atm) expressed per atmosphere 10^{-8} of hydrostatic or osmotic pressure difference across the semi-permeable wall. The polymers are known to the art in U.S. Pat. Nos. 3,845,770; 3,916,899; and 4,160,020; and in *Handbook of Common Polymers* by Scott, J. R. and Roff, W. J., 1971 published by CRC Press, Cleveland, Ohio.

The laminated wall comprising a semi-permeable lamina and a microporous lamina are in laminar arrangement and they act in concert to form an integral laminated wall, that maintains its physical and chemical integrity and does not separate into lamina through the operative agent release history of an osmotic device. The semi-permeable lamina is made from the semi-permeable polymeric materials presented above, the semi-permeable homopolymers, the semi-permeable copolymers and the like.

Microporous lamina suitable for manufacturing an osmotic device generally comprises performed microporous polymeric materials, and polymeric materials that can form a microporous lamina in the environment of use. The microporous materials in both embodiments are laminate to form the laminate wall. The preformed materials suitable for forming the microporous lamina are essentially inert, they maintain their physical and chemical integrity during the period of agent release and they can be generically described as having a sponge-like appearance that provides a supporting structure for a semi-permeable lamina and also provide a supporting structure for microscopic-sized interconnected pores or voids. The materials can be isotropic wherein the structure is homogenous throughout a cross-sectional area, or they can be anisotropic wherein the structure is non-homogenous throughout a cross-sectional area. The pores can be continuous pores that have an opening on both faces of a microporous lamina, pores interconnected through tortuous paths of regular and irregular shapes including curved, curved-linear, randomly oriented continuous pores, hindered connected pores and other porous paths discernible by microscopic examination. Generally, microporous lamina are defined by the pore size, the number of pores, the tortuosity of the microporous path and the porosity which relates to the size and the number of pores. The pore size of a microporous lamina is easily ascertained by measuring the observed pore diameter at the surface of the material under the electron microscope. Generally, materials possessing from 5% to 95% pores and having a pore size of from 10 angstroms to 100 microns can be used for making a microporous lamina. The pore size and other parameters characterizing the microporous structure also can be obtained from flow measurements, where a liquid

flux, J, is produced by a pressure difference ΔP, across the lamina. The liquid flux through a laminate with pores of uniform radius extended through the membrane and perpendicular to its surface with area A is given by relation 13:

$$J=\frac{N\pi^4\Delta P}{8\eta\Delta x} \qquad (13)$$

wherein J is the volume transported per unit time and lamina area containing N number of pores of radius r, η is the viscosity of the liquid, and ΔP is the pressure difference across the lamina with thickness Δx. For this type of lamina, the number of pores N can be calculated from relation 14, wherein ε is the porosity defined as the ratio of void volume to total volume of the lamina: and A is the cross-sectional area of the lamina containing N pores.

$$N=\frac{\varepsilon A}{\pi r^2} \qquad (14)$$

The pore radius then is calculated from relation 15:

$$r=8\eta\frac{\Delta x\,\tau}{\Delta p\,\varepsilon} \qquad (15)$$

wherein J is the volume flux through the lamina per unit area produced by the pressure difference ΔP across the lamina, η, ε and Δx have the meaning defined above and τ is the turtuosity defined as the ratio of the diffusional path length in the lamina to the lamina thickness. Relations of the above type are discussed in *Transport Phenomena In Membranes*, by Lakshiminatayanaiah, N, Chapter 6, 1969, published by Academic Press, Inc., New York.

As discussed in this reference on page 336, in Table 6.13, the porosity of the lamina having pores with radius r can be expressed relative to the size of the transported molecule having a radius a, and as the ratio of molecular radius to pore radius a/r decreases, the lamina becomes porous with respect to this molecule. That is, when the ratio a/r is less than 0.3, the lamina becomes substantially microporous as expressed by the osmotic reflection coefficient σ which decreases below 0.5. Microporous lamina with a reflection coefficient σ in the range of less than 1, usually from 0 to 0.5 and preferably less than 0.1 with respect to the active agent are suitable for fabricating the system. The reflection coefficient is determined by shaping the material in the form of a lamina and carrying out water flux measurements as a function of hydrostatic pressure difference and as a function of the osmotic pressure difference caused by the active agent. The osmotic pressure difference creates a hydrostatic volume flux, and the reflection coefficient is expressed by relation 16:

$$\sigma=\frac{\text{osmotic volume flux}}{\text{hydrostatic volume flux}} \qquad (16)$$

Properties of microporous materials are described in *Science*, Vol. 170 pages 1302 to 1305, 1970; *Nature*, Vol. 214 page 285, 1967; *Polymer Engineering and Science* Vol. 11 pages 284—288, 1971; U.S. Pat. Nos. 3,567,809 and 3,751,536; and in *Industrial Processing With Membranes* by Lacey R. E. and Loeb Sidney pages 131 to 134, 1972, published by Wiley, Interscience, New York.

Microporous materials having a preformed structure are commercially available and they can be made by art-known methods. The microporous materials can be made by etching, nuclear tracking, by cooling a solution of flowable polymer below the freezing point whereby solvent evaporates from the solution in the form of crystals dispersed in the polymer and then curing the polymer followed by removing the solvent crystals, by cold or hot stretching at low or high temperatures until pores are formed, by leaching from a polymer a soluble component by an appropriate solvent, by ion exchange reaction, and by polyelectrolyte processes. Processes for preparing microporous materials are described in *Synthetic Polymer Membranes*, by R. E. Kesting, Chapters 4 and 5, 1971 published by McGraw Hill, Inc.; *Chemical Reviews*, Ultrafiltration, Vol. 18, pages 373 to 455, 1934; *Polymer Eng. and Sci.*, Vol. 11, No. 4, pages 284 to 288, 1971; *J. Appl. Poly Sci.*, Vol. 15, pages 811 to 829, 1971; and in U.S. Pat. Nos. 3,565,259; 3,615,024; 3,751,536; 3,801,692; 3,852,224 and 3,849,528.

Microporous materials useful for making the lamina include microporous polycarbonates comprises of linear polyesters of carbonic acid in which carbonate groups recur in the polymer chain, microporous materials prepared by the phosgenation of a dihydroxyl aromatic such as bisphenol A, microporous poly(vinylchloride), microporous polyamides such as polyhexamethylene adipamide, microporous modacrylic copolymers including those formed from poly(vinylchloride) 60% and

acrylonitrile, styrene-acrylic and its copolymers, porous polysulfones characterised by diphenylene sulfone groups in a linear chain thereof, halogenated poly(vinylidene), polychloroethers, acetal polymers, polyesters prepared by exterification of a dicarboxylic acid or anhydride with an alkylene polyol, poly(alkylenesulfides), phenolic polyesters, microporous poly(saccharides), microporous poly(saccharides) having substituted and unsubstituted anhydroglucose units and preferably exhibiting an increased permeability to the passage of water and biological fluids than semi-permeable lamina, asymmetric porous polymers, cross-linked olefin polymers, hydrophobic or hydrophilic microporous homopolymers, copolymers or interpolymers having a reduced bulk density, and materials described in U.S. Pat. Nos. 3,597,752; 3,643,178; 3,654,066; 3,709,774; 3,718,532; 3,803,061; 3,852,224; 3,853,601; and 3,852,388 in British Pat. No. 1,126,849 and in *Chem. Abst.*, Vol. 71 4274F, 22572F, 22573F, 1969.

Additional microporous materials include poly(urethanes), cross-linked, chain-extended poly(urethanes), microporous poly(urethanes) in U.S. Pat. No. 3,524,753 poly(imides), poly(benzimidazoles), collodion (cellulose nitrate with 11% nitrogen), regenerated proteins, semi-solid cross-linked poly(vinylpyrrolidone), microporous materials prepared by diffusion of multivalent cations into polyelectrolyte sols as in U.S. Pat. No. 3,565,259, anisotropic permeable microporous materials of ionically associated polyelectrolytes, porous polymers formed by the coprecipitation of a polycation and a polyanion as described in U.S. Pat. Nos. 3,276,589; 3,541,055; 3,541,066 and 3,546,142 derivatives of poly(styrene) such as poly(sodium styrenesulfonate) and poly(vinyl benzyltrimethyl-ammonium chloride), the microporous materials disclosed in U.S. Pat. No. 3,615,024 and U.S. Pat. Nos. 3,646,178 and 3,852,224.

Further, the microporous forming material used for the purpose of the invention, includes the embodiment wherein the microporous lamina is formed in situ, by a pore-former being removed by dissolving or leaching it to form the microporous lamina during the operation of the system. The pore-former can be a solid or a liquid. The term liquid, for this invention, embraces semi-solids and viscous fluids. The pore-formers can be inorganic or organic. The pore-formers suitable for the invention include pore-formers that can be extracted without any chemical change in the polymer. The pore-forming solids have a size of about 0.1 to 200 micrometres and they include alkali metal salts such as sodium chloride, sodium bromide, potassium chloride, potassium sulfate, potassium phosphate, sodium benzoate, sodium acetate, sodium citrate, potassium nitrate and the like. The alkali earth metal salts include calcium phosphate, calcium nitrate and the like. The transition metal salts include ferric chloride, ferrous sulfate, zinc sulfate, cupric chloride, manganese fluoride, manganese fluorosilicate, and the like. The pore-formers include organic compounds such as polysaccharides. The polysaccharides include the sugars sucrose, glucose, fructose, mannitol, mannose, galactose, aldohexose, altrose, talose, sorbitol, lactose, monosaccharides and disaccharides. Also, organic aliphatic and aromatic oils and solids, including diols and polyols, as exemplified by polyhydric alcohols, poly(alkylene glycols), polyglycols, alkylene glycols, poly(α-ω)-alkylenediols esters or alkylene glycols and the like; water soluble cellulosic polymers such as hydrosyloweralkyl cellulose, hydroxypropyl methylcellulose, methyl cellulose, methylethyl cellulose, hydroxyethyl cellulose and the like; water soluble polymers such as polyvinylpyrrolidone, sodium carboxymethylcellulose and the like. The pore-formers are nontoxic and on their removal form the lamina channels are formed through the lamina. In a preferred embodiment, the nontoxic pore-forming agents are selected from the group consisting of inorganic and organic salts, carbohydrates, polyalkylene glycols, poly(α-ω)-alkylenediols, esters of alkylene glycols, glycols, and water soluble cellulosic polymers, useful for forming a microporous lamina in a biological environment. Generally, for the purpose of this invention, when the polymer forming the lamina contains more than 25% by weight of a pore-former, the polymer is a precursor microporous lamina that on removing the pore-former, yields a lamina which is substantially microporous, at concentrations less than this, the lamina behaves like a semi-permeable lamina or membrane.

The expression passageway as used comprises means and methods suitable for releasing the agent or drug from the osmotic system. The expression includes aperture, orifice, hole, or bore through the semi-permeable wall or the laminated wall. The passageway can be formed by mechanical drilling, laser drilling, or by eroding an erodible element, such as a gelatin plug, in the environment of use. A detailed description of osmotic passageways, and the maximum and minimum dimensions for a passageway are disclosed in United States Pat. Nos. 3,845,770 and 3,916,899.

The osmotically effective compounds that can be used for the purpose of this invention include inorganic and organic compounds that exhibit an osmotic pressure gradient across a semi-permeable wall, or across a semi-permeable microporous laminated wall, against an external fluid. The osmotically effective compounds (along with the osmopolymers) imbibe fluid into the osmotic device thereby making available in situ fluid for imbibition by an osmopolymer to enhance its expansion, and/or for forming a solution or suspension containing a beneficial agent for its delivery from the osmotic device. The osmotically effective compounds are known also as osmotically effective solutes, or osmagents. The osmotically effective compounds are used by mixing them with a beneficial agent and osmopolymer for forming a solution, or suspension containing the beneficial agent that is osmotically delivered from the device. The expression limited solubility as used herein means the agent has a solubility of about less than 5% by weight in the aqueous fluid present in the environment. The osmotic

solutes are used by homogenously or heterogenously mixing the solute with the agent or osmopolymer, and then charging them into the reservoir. The solutes and osmopolymers attract fluid into the reservoir producing a solution of solute in a gel which is delivered from the system concomitantly transporting undissolved and dissolved beneficial agent to the exterior of the system. Osmotically effective solutes used for the former purpose include magnesium sulfate, magnesium chloride, sodium chloride, potassium chloride, lithium chloride, potassium sulfate, sodium sulfate, lithium chloride, potassium sulfate, sodium sulfate, lithium sulfate, potassium acid phosphate, d-mannitol, urea, inositol, magnesium succinate, tartaric acid, carbohydrates such as raffinose, sucrose, glucose, α-d-lactose monohydrate, and mixtures thereof. The amount of osmagent in the compartment will generally be from 0.01% to 30%, or higher in the first composition, and usually from 0.01% to 40% or higher in the second compartment.

The osmotic solute is initially present in excess and it can be in any physical form that is compatible with the beneficial agent and the osmagent. The osmotic pressure of saturated solutions of various osmotically effective compounds and for mixtures of compounds at 37°C, in water, is listed in Table 1. In the table, the osmotic pressure π, is in atmospheres, ATM. The osmotic pressure is measured in a commercially available osmometer that measures the vapor pressure difference between pure water and the solution to be analyzed, and according to standard thermodynamic principles, the vapor pressure ratio is converted into osmotic pressure difference. In Table 1, osmotic pressures of from 20 ATM to 500 ATM are set forth; of course, the invention includes the use of lower osmotic pressures from zero, and higher osmotic pressures than those set forth by way of example in Table 1. The osmometer used for the present measurements is identified as Model 320B, Vapor Pressure Osmometer, manufactured by the Hewlett Packard Co., Avonadale, Penna.

TABLE 1

Compound or Mixture	Osmotic Pressure ATM
Lactose-Fructose	500
Dextrose-Fructose	450
Sucrose-Fructose	430
Mannitol-Fructose	415
Sodium Chloride	356
Fructose	355
Lactose-Sucrose	250
Potassium Chloride	245
Lactose-Dextrose	225
Mannitol-Dextrose	225
Dextrose-Sucrose	190
Mannitol-Sucrose	170
Dextrose	82
Potassium Sulfate	39
Mannitol	38
Sodium Phosphate Tribasic · $12H_2O$	36
Sodium Phosphate Dibasic · $7H_2O$	31
Sodium Phosphate Dibasic · $12H_2O$	31
Sodium Phosphate Dibasic Anhydrous	29
Sodium Phosphate Monobasic · H_2O	28

The osmopolyers suitable for forming the first osmotic composition, and also suitable forming the second osmotic composition are osmopolymers that exhibit fluid imbibition properties. The osmopolymers are swellable, hydrophilic polymers which interact with water and aqueous biological fluids and swell, or expand to an equilibrium state. The osmopolymers exhibit the ability to swell in water and retain a significant portion of the imbibed water within the polymer structure. The osmopolymers swell or expand to a very high degree, usually exhibiting a 2 to 50 fold volume increase. The swellable, hydrophilic polymers are in one presently preferred embodiment lightly cross-linked, such cross-links being formed by covalent or ionic bonds. The osmopolymers can be of plant, animal, or synthetic origin. The osmopolymers are hydrophilic polymers. Hydrophilic polymers suitable for the present purpose include poly(hydroxyalkyl methacrylate) having a molecular weight of from 30,000 to 5,000,000; poly(vinylpyrrolidone) having a molecular weight of from 10,000 to 360,000; anionic and cationic hydrogels; polyelectrolyte complexes; poly(vinyl alcohol) having a low acetate residual, cross-linked with glyoxal, formaldehyde, or glutaraldehyde and having a degree of polymerization from 200 to 30,000; a mixture of methyl cellulose, cross-linked agar and carboxymethyl cellulose; a water-insoluble, water-swellable copolymer produced by forming a dispersion of finely divided copolymer of maleic anhydride with styrene ethylene, propylene, butylene or isobutylene cross-linked with from 0.001 to about 0.5 moles of polyunsaturated cross-linking agent per mole of maleic anhydride in the copolymer; water-swellable polymers of N-vinyl lactams and the like.

Other osmopolymers include polymers that form hydrogels such as Carbopol acidic carboxy polymers having a molecular weight of 450,000 to 4,000,000; Cyanamer polyacrylamides; cross-linked water-swellable indene-maleic anhydride polymers; Good-rite polyacrylic acid having a molecular weight of 80,000 to 200,000; Polyox polyethylene oxide polymers having a molecular weight of 100,000 to 5,000,000; starch graft copolymers; Aqua-Keeps acrylate polymer; diester cross-linked polyglucan; and the like. Representative polymers that form hydrogels are known to the prior art in U.S. Pat. No. 3,865,108 issued to Hartop; U.S. Pat. No. 4,002,173 issued to Manning; U.S. Pat. No. 4,207,893 issued to Michaels; and in *Handbook of Common Polymers* by Scott and Roff, published by the Chemical Rubber Co., Cleveland, Ohio. The amount of osmopolymer in the first osmotic composition is about .01 to 90% and the amount of osmopolymer in the second osmotic composition is 15 to 95%. In a presently preferred embodiment, the molecular weight of the osmopolymer in the second osmotic composition is larger than the molecular weight of the osmopolymer in the first osmotic composition.

Osmopolymer fluid imbibition determination for a chosen polymer can be made by following the procedure described below. A 1/2 inch round disc, fitted with a 1/2 inch diameter stainless steel plug, is charged with a known quantity of polymer with the plugs extending out either end. The plugs and the die were placed in a Carver press with plates between 200° and 300°F. A pressure of 10,000 to 15,000 PSI was applied to the plugs. After 10 to 20 minutes of heat and pressure, the electrical heating to the plates were turned off, and tap water circulated through the plates. The resulting 1/2 inch discs were placed in an air suspension coater charged with 1.8 kg saccharide cores and coated with cellulose acetate having an acetyl content of 39.8% dissolved in 94:6 w/w, CH_2Cl_2/CH_3OH, to yield a 3% w/w solution. The coated systems were dried overnight at 50°C the coated discs were immersed in water at 37°C and periodically removed for a gravimetric determination of water imbibed. The initial imbibition pressure was calculated by using the water transmission constant for the cellulose acetate, after normalizing imbibition values for membrane surface area and thickness. The polymer used in this determination was the sodium derivative of Carbopol-934 polymer, prepared according to the procedure of B. F. Goodrich Service Bulletin GC-36, "Carbopol Water-Soluble Resins", page 5, published by B. F. Goodrich, Akron, Ohio. The cumulative weight gain values, y, as a function of time, t, for the water soluble polymer disc coated with the cellulose acetate were used to determine the equation of the line $y=c+bt+at^2$ passing through those points by a least square fitting technique.

The weight gain for the Na Carbopol-934 is given by the equation 17 that follows: Weight Gain equals $0.359+0.665t-0.00106t^2$ wherein t is elapsed time in minutes. The rate of water flux at any time will be equal to the slope of the line, that is given by the following equation 18 and 19:

$$\frac{dy}{dt} = \frac{d(0.359+0.665t-0.00106t^2)}{dt} \qquad (18)$$

$$\frac{dy}{dt} = 0.665-0.00212t \qquad (19)$$

To determine the initial rate of water flux the derivative is evaluated at t=0, and dy/dt=0.665 μl/min, which is equal to the coefficient b. Then, normalizing the imbibition rate for time, membrane surface area and thickness, and the membrane permeability constant to water, K, π may be determined according to the following equation 20:

$$K\pi = 0.665\ \mu l/min \times \left(\frac{60\ min}{hr}\right) \times \left(\frac{1\ ml}{1000\ \mu l}\right)\left(\frac{0.008\ cm}{2.86\ cm^2}\right) \quad (20)$$

with $K=1.13\times10^{-4}$ cm²/hr. The (π) value for NaCl was determined with a Hewlett-Packard vapor pressure osmometer to be 345 atm±10%, and the K value for cellulose acetate used in this experiment calculated from NaCl imbibition values was determined to be 1.9×10^{-7} cm²/hr atm.

Substituting these values into the calculated Kπ expression (1.9×10^{-7}/cm²/hr.atm) (π)=1.13×10^{-4} cm²/hr gives π=600 atm at t=0. As a method for evaluating the efficiency of a polymer with respect to duration of zero-order driving force, the % of water uptake was selected before the water flux values decreased to 90% of their initial values. The value of the slope for the equation of a straight line emanating from the % weight gained axis will be equal to the initial value of dy/dt evaluated at t=0, with the y intercept c defining the linear swelling time, with (dy/dt) 0=0.665 and y intercept=0, which yields y=0.665t+0.359. In order to determine when the value of the cumulative water uptake is 90% below the initial rate, the following expression is solved for t,

$$0.9=\frac{at^2+bt+c}{bt+c}=\frac{\Delta W}{w}0.9 \quad (21)$$

$$\frac{-0.00106t^2+0.665t+0.359}{0.665t+0.359}=0.9, \text{ and} \quad (22)$$

solving for t,

$$-0.00106t^2+0.0665t+0.0359=0$$

$$t=\frac{-0.0665\pm[(0.0665)^2-4(-0.00106)(0.0359)]^{1/2}}{2(-0.00106)} \quad (23)$$

t=62 min and the weight gain is $-0.00106(62)^2+(0.665)(62)+0.359=38\ \mu l$, with the initial sample weight=100 mg, thus (Δw/w) 0.9×100=38%. The results are presented in Figure 8 for a graphical representation of the values. Other methods available for studying the hydrogel solution interface include rheologic analysis, viscometric analysis, ellipsometry, contact angle measurements, electrokinetic determinations, infrared spectroscopy, optical microscopy, interface morphology and microscopic examination of an operative device.

The expression active agent as used herein, includes any beneficial agent, or beneficial compound, that can be delivered from the device to produce a benefical and useful result. The agent can be insoluble to very soluble in the exterior fluid that enters the device and it can be mixed with an osmotically effective compound and an osmopolymer. The term active agent includes pesticides, herbicides, germicides, biocides, algicides, rodenticides, fungicides, insecticides, antioxidants, plant growth, promoters, plant growth inhibitors, preservatives, disinfectants, sterilization agents, catalysts, chemical reactants, fermentation agents, sex sterilants, fertility inhibitors, fertility promoters, air purifiers, micro-organism attenuators, and other agents that benefit the environment of use.

In the specification and the accompanying claims, the term beneficial agent includes drug, and the term drug includes any physiologically or pharmacologically active substance that produces a local or systemic effect, in animals, including warm blooded mammals, humans and primates, avians, household, sport and farm animals, laboratory animals, fishes, reptiles and zoo animals. The term physiologically as used herein denotes the administration of a drug to produce normal levels and functions. The term pharmacologically denotes variations in response to amount of drug administered to the host. See *Stedman's Medical Dictionary*; 1966 published by Williams and Wilkins, Baltimore, Md. The phrase drug formulation as used herein means the drug is in the compartment mixed with an osmotic solute and/or an osmopolymer and if applicable, and with a binder and lubricant. The active drug that can be delivered includes inorganic and organic compounds without limitation, including drugs that act on the peripheral nerves, adrenergic receptors, cholinergic receptors, nervous system, skeletal muscles, cardiovascular system, smooth muscles, blood circulatory system, synoptic sites, neuroeffector junctional sites, endocrine system, hormone systems, immunological system, organ systems, reproductive system, skeletal system, autocoid systems, alimentary and excretory systems, inhibitory of autocoids and histamine systems. The active drug that can be delivered for acting on these animal systems includes depressants, hypnotics, sedatives, psychic energizers, tranquilizers, anticonvulsants, muscle relaxants, antiparkinson agents, analgesics, anti-inflammatory, local anesthetics, muscle contractants, anti-microbials, anti-malarials, hormonal agents, contraceptives, sympathomimetics, diuretics, anti-parasitics, neoplastics, hypoglycemics, ophthalmics, electrolytes, diagnostic agents and cardiovascular drugs.

Exemplary drugs that are very soluble in water and can be delivered by the devices of this

invention include prochlorperazine edisylate, ferrous sulfate, aminocaproic acid, potassium chloride, mecamylamine hydrochloride, procainamide hydrochloride, amphetamine sulfate, benzphetamine hydrochloride, isoproternol sulfate, methamphetamine hydrochloride, phenmetrazine hydrochloride, bethanechol chloride, mechacholine chloride, pilocarpine hydrochloride, atropine sulfacte, methascopolamine bromide, isopropamide iodide, tridihexethyl chloride, phenformin hydrochloride, methylphenidate hydrochloride, oxprenolol hydrochloride, metoprolol tartrate, imetidine hydrochloride, theophylline cholinate, cephalexin hydrochloride and the like.

Exemplary drugs that are poorly soluble in water and that can be delivered by the devices of this invention include diphenidol, meclizine hydrochloride, prochlorperazine maleate, phenoxybenzamine, thiethylperazine maleate, anisindone, diphenadione erythrityl tetranitrate, dizoxin, isofurophate, reserpine, acetazolamide, ethazolamide, bendroflumethiazide, chlorpropamide, tolazamide, chlormadinone acetate, phenaglycodol, allopurinol, aluminum aspirin, methotrexate, acetyl sulfisoxazole, erythromycin, profestins, esterogenic progestational, corticosteroids, hydrocortisone, hydrocorticosterone acetate, cortisone acetate, triamcinolone, methyltesterone 17β-estradiol, ethinyl estradiol, prazosin hydrochloride ethinyl estradiol 3-methyl ether, prednisolone, 17β-hydroxyprogesterone acetate, 19-nor-progesterone, norgestrel, norethiderone, progesterone, norgesterone, norethynodrel and the like.

Examples of other drugs that can be delivered by the osmotic device include aspirin, indomethacin, naproxen, fenoprofen, sulidac, diclofenac, indoprofen, nitroglycerin, propanolol, metoprolol, valproate, oxprenolol, timolol, atenolol, alprenolol, cimetidine, imipramine, levodopa, chloropromazine, reserpine, methyl-dopa, dihydroxyphenylalanine, pivaloyloxyethyl, ester of α-methyldopa hydrochloride, theophylline, calcium gluconate, ketoprofen, ibuprofen, cephalexin, erythromycin, proszin, haloperidol, zomepirac, ferrous lactate, vincamine, diazepam, phenoxybenzamine, α-blocking agents, calcium-channel blocking drugs such as nifedipine, diliazen, verapamil, betablockers and the like. The beneficial drugs are known to the art in *Pharmaceutical Sciences,* edited by Remington 14th Ed., 1979 published by Mack Publishing Co., Easton, Penna.; *The Drug, The Nurse, The Patient, Including Current Drug Handbook,* 1974—1976 by Falconer, et al., published by Saunder Company, Philadelphia, Penna.; and *Medicinal Chemistry,* 3rd Ed., Vol. 1 and 2 by Burger, published by Wiley-Interscience, New York.

The drug can be in various forms, such as uncharged molecules, molecular complexes, pharmacologically acceptable salts such as hydrochloride, hydrobromide, sulfate, laurylate, palmitate, phosphate, nitrite, borate, acetate, maleate, tartrate, oleate and salicylate. For acidic drugs, salts of metals, amines or organic cations, for example quaternary ammonium, can be used. Derivatives of drugs such as esters, ethers and amides can be used. Also, a drug that is water insoluble can be used in a form that is a water soluble derivative thereof to serve as a solute and on its release from the device, is converted by enzymes, hydrolyzed by body pH or other metabolic processes to the original biologically active form. The agent including drug, can be present in the compartment with a binder, dispersant, wetting agent, suspending agent, lubricant and dye. Representative of these include suspending agents such as acacia, agar, calcium carrageenan, alginic acid, algin, agarose powder, collagent, colloidal magnesium silicate, colloidal silicon dioxide, hydroxyethyl cellulose, pectin, gelatin and calcium silicate; binders like polyvinyl pyrrolidone, lubricants such as magnesium stearate, wetting agents such as fatty amines, fatty quaternary ammonium salts and the like. The phrase drug formulation indicates the drug is present in the compartment accompanied by an osmagent, osmopolymer, a binder and the like. The amount of beneficial agent in a device generally is about from 0.05 ng to 5 g or more, with individual devices containing for example, 25 ng, 1 mg, 5 mg, 125 mg, 250 mg, 500 mg, 750 mg, 1.5 g, and the like. The devices can be administered once, twice or thrice daily.

The solubility of a beneficial agent in the fluid can be determined by known techniques. One method consists of preparing a saturated solution comprising the fluid plus the agent as ascertained by analyzing the amount of agent present in a definite quantity of the fluid. A simple apparatus for this purpose consists of a test tube of medium size fastened upright in a water bath maintained at constant temperature and pressure, in which the fluid and agent are placed and stirred by a rotating glass spiral. After a given period of stirring, a weight of the fluid is analyzed and the stirring continued an additional period of time. If the analysis shows no increase of dissolved agent after successive period of stirring, in the presence of excess solid agent in the fluid, the solution is saturated and the results are taken as the solubility of the product in the fluid. If the agent is soluble, an added osmotically effective compound optionally may not be needed; if the agent has limited solubility in the fluid, then an osmotically effective compound can be incorporated into the device. Numerous other methods are available for the determination of the solubility of an agent in a fluid. Typical methods used for the measurement of solubility are chemical and electrical conductivity. Details of various methods for determining solubilities are described in United States *Public Health Service Bulletin,* No. 67 of the Hygenic Laboratory; *Encyclopedia of Science and Technology,* Vol. 12, pages 542 to 556, 1971, published by McGraw-Hill, Inc., and *Encyclopedia Dictionary of Physics,* Vol. 6, pages 547 to 557, 1962 published in Pergamon Press, Inc.

The osmotic devices of the invention is manufactured by standard techniques. For example, in

one embodiment, the beneficial agent is mixed with an osmagent and osmopolymer, and pressed into a solid possessing dimensions that correspond to the internal dimensions of the compartment adjacent to the passageway; or the beneficial agent and other formulation forming ingredients and a solvent are mixed into a solid or a semisolid by conventional methods such as ballmilling, calendering, stirring or rollmilling and then pressed into a preselected shape. Next, a layer of a composition comprising an osmagent and an osmopolymer is placed in contact with the layer of beneficial agent formulation, and the two layers surrounded with a semi-permeable wall. The layering of the beneficial agent composition and the osmagent/osmopolymer can be accomplished by conventional two-layer tablet press techniques. The wall can be applied by molding, spraying or dipping the pressed shaped into wall-forming material. Another and presently preferred technique that can be used for applying the wall is the air suspension coating procedure. This procedure consists in suspending and tumbling the pressed compositions in a current of air and a wall forming composition until the wall surrounds and coats the two pressed compositions. The procedure is repeated with a different lamina forming composition to form a laminated wall. The air suspension procedure is described in U.S. Pat. No. 2,799,241; *J. Am. Pharm. Assoc.*, Vol. 48, pages 451 to 459, 1979; and ibid, Vol. 49, pages 82 to 84, 1960. Other standard manufacturing procedures are described in *Modern Plastics Encyclopedia,* Vol. 46, pages 62 to 70, 1969; and in *Pharmaceutical Sciences,* by Remington, 14th Edition, pages 1626 to 1678, 1970, published by Mack Publishing Co., Easton, Penna.

Exemplary solvents suitable for manufacturing the laminates and laminae include inert inorganic and organic solvents that do not adversely harm the materials and the final laminated wall. The solvents broadly include members selected from the group consisting of aqueous solvents, alcohols, ketones, esters, ethers, aliphatic hydrocarbons, halogenated solvents, cycloaliphatics, aromatics, heterocyclic solvents and mixtures thereof. Typical solvents include acetone, diacetone alcohol, methanol, ethanol, isopropyl alcohol, butyl alcohol, methyl acetate, ethyl acetate, isopropyl acetate, n-butyl acetate, methyl isobutyl ketone, methyl propyl ketone, n-hexane, n-heptane, ethylene glycol monoethyl ether, ethylene glycol monoethyl acetate, methylene dichloride, ethylene dichloride, propylene dichloride, carbon tetrachloride, chloroform nitroethane, nitropropane, tetrachloroethane, ethyl ether, isopropyl ether, cyclohexane, cyclooctane, benzene, toluene, naphtha, 1,4-dioxane, tetrahydrofuran, diglyme, water and mixtures thereof such as acetone and water, acetone and methanol, acetone and ethyl alcohol, methylene dichloride and methanol, and ethylene dichloride and methanol.

Detailed Description of Examples

The following examples are merely illustrative of the present invention, and they should not be considered as limiting the scope of the invention in any way, as these examples and other equivalents thereof will become apparent to those versed in the art in the light of the present disclosure, the drawings and the accompanying claims.

EXAMPLE 1

An osmotic delivery device manufactured as an osmotic tablet shaped, sized and adapted for oral admittance into the gastrointestional tract is made as follows: a first osmotic drug composition is prepared by screening 355 g of poly(ethylene oxide) having an approximate molecular weight of 200,000 through a 40 mesh stainless steel screen, then 100 g of nifedipine is passed through the 40 mesh screen, 25 g of hydroxypropylmethylcellulose is passed through the 40 mesh screen, and finally 10 g of potassium chloride is passed through the 40 mesh screen. Next, all the screened ingredients are added to the blowl of a laboratory blender and the ingredients dry blended for 15—20 minutes to produce a homogeneous blend. Then a granulation fluid is prepared comprising 250 ml of ethanol and 250 ml of isopropyl alcohol and the granulating fluid added to the blending blowl; a first 50 ml is sprayed into the bowl with constant blending then 350 ml of the granulation fluid is added slowly to the bowl and the wet mass blended for another 15 to 20 minutes. Then the wet granules are passed through a 16 mesh screen and dried at room temperature for 24 hours, and the dry granules passed through a 16 mesh screen. Next, 10 g of magnesium stearate is added to the dry granules, and the ingredients roll-mixed for 20—30 minutes on a standard two roll mill.

Next, a second osmotic composition is prepared as follows: first, 170 g of poly(ethylene oxide) having a molecular weight of 5,000,000 is screened through a 40 mesh screen, then 72.5 g of sodium chloride is passed through the 40 mesh screen and the ingredients added to a mixing bowl and blended for 10—15 minutes. Then a granulation fluid is prepared by mixing 350 ml of methanol and 150 ml of isopropyl alcohol and the granulation fluid added to the blending bowl in two steps. First, 50 ml of the granulation fluid is sprayed into the bowl with constant blending, then 350 ml of the granulation fluid is slowly added to the bowl and the wet blend mixed for 15—20 minutes to a homogeneous blend. Then, the wet blend is passed through a 16 mesh screen, spread on a stainless steel tray and dried at room temperature of 22.5°C for 24 hours. The dried blend is passed through a 16 mesh screen, the roll milled with 5 g of magnesium stearate on a two roll mill for 20—30 minutes.

A number of drug cores are prepared by pressing the two compositions on Manesty Layerpress. The drug containing composition is fed into the cavity mold of the press and compressed into a solid

layer. Then, the second osmotic composition is fed into the cavity overlaying the compressed layer and pressed into a solid layer to form a two layered drug core.

The drug cores next are coated with a semi-permeable wall-forming composition comprising 95 g of cellulose acetate having an acetyl content of 39.8% and 5 g of poly(ethylene glycol) 4000 in a solvent comprising 1960 ml of methylene chloride and 820 ml of methanol. The drug cores are coated with the semi-permeable wall forming composition until the wall surrounds the drug core. A Wurster air suspension coater is used to form the semi-permeable wall. The coated cores are then spread on a tray and the solvent evaporated in a circulating air oven at 50°C for 65 hours. After cooling to room temperature a 0.26 mm diameter passageway is laser drilled through the semi-permeable wall connecting the exterior of the osmotic device with the composition containing the drug. The osmotic device weighed 262 mg and it contained 30 mg of drug in the first composition weighing 150 mg, the second composition weighed 75 mg and the semi-permeable wall weighed 37 mg. The first osmotic composition of the osmotic device comprises 30 mg of nifedipine, 106 mg of poly(ethylene oxide), 3 mg of potassium chloride, 7.5 mg of hydroxypropylmethylcellulose and 3 mg of magnesium stearate. The second osmotic composition comprises 51 mg of poly(ethylene oxide), 22 mg of sodium chloride, and 1.5 mg of magnesium stearate. The device has a diameter of 8 mm, a surface area of 1.8 cm^2 and the semi-permeable wall is 0.17 mm thick. The cumulative amount of drug released is depicted in Figure 9.

EXAMPLE 1A

Osmotic delivery systems are prepared having a first composition comprising 25 to 100 mg of nifedipine, 100 to 325 mg of poly(ethylene oxide) having a molecular weight of 200,000, 2 to 10 mg of potassium chloride, 5 to 30 mg of hydroxypropylmethylcellulose and 2 to 10 mg of magnesium stearate; and a second composition comprising 30 to 175 mg of poly(ethylene oxide) having a molecular weight of 5,000,000, 20 to 75 mg of sodium chloride and 1 to 5 mg of magnesium stearate. The procedure of Example 1 is repeated for preparing osmotic devices having the following compositions: (a) an osmotic device having a first composition comprising 60 mg of nifedipine, 212 mg of poly(ethylene oxide), 6 mg of potassium chloride, 15 mg of hydroxypropylmethylcellulose and 6 mg of magnesium stearate; and a second composition comprising 102 mg of poly(ethylene oxide), 44 mg of sodium chloride, and 3 mg of magnesium stearate; and (b) an osmotic device having a first composition comprising 90 mg of nifedipine, 318 mg of poly(ethylene oxide), 9 mg of potassium chloride, 22.5 mg of hydroxypropylmethylcellulose, and 9 mg of magnesium stearate, and a second composition comprising 102 mg of poly(ethylene oxide), 66 mg of sodium chloride, and 4.5 mg of magnesium stearate. In an embodiment, the osmotic device described in (a) and (b) further comprise a pulse coated on the outer semi-permeable wall. The pulse coat comprises 30 mg of nifedipine and hydroxypropylmethylcellulose. In operation in the fluid environment of use, the pulse coat provides instant drug availability for instant drug therapy.

EXAMPLE 2

The procedure of Example 1 is repeated with all conditions as previously described except that the drug in the compartment is replaced with a member from the group consisting of a beta-blocker, anti-inflammatory, analgesic, sympathomimetic, antiparkinson or a diuretic drug.

EXAMPLE 3

An osmotic therapeutic device for the controlled and the continuous oral release of the beneficial calcium channel blocker drug verapamil is made as follows: 90 mg of verapamil, 50 mg of sodium carboxyvinyl polymer having a molecular weight of 200,000 and sold under the trademark Carbopol® polymer, 3 mg of sodium chloride, 7.5 mg of hydroxypropylmethylcellulose and 3 mg of magnesium stearate are mixed thoroughly as described in Example 1, and pressed in a Manesty press with a 5/16 inch punch using a pressure head of 1-1/2 tons to produce a layer of the drug composition. Next, 51 mg of the carboxyvinyl polymer having a molecular weight of 3,000,000 and sold under the trademark Carbopol® polymer 22 mg of sodium chloride and 2 mg of magnesium stearate are blended thoroughly and added to the Manesty press, and pressed to form a layer of expandable, osmotic composition in contact with the layer of osmotic drug composition.

Next, a semi-permeable wall is formed by blending 170 g of cellulose acetate having an acetyl of 39.8% with 900 ml of methylene chloride and 400 ml of methanol and spray coating the two layered compartment forming member in an air suspension machine until a 5.1 mil thick semi-permeable wall surrounds the compartment. The coated device is dried for 72 hours at 50°C and then a 8 mil passageway is laser-drilled through the semi-permeable wall to connect the layer containing drug with the exterior of the device for releasing drug over a prolonged period of time.

EXAMPLE 4

The procedure of Example 3 is repeated with all conditions as described except that the drug in the osmotic device is fendiline, diazoxide, prenylamine or diltiazen.

EXAMPLE 5

An osmotic, therapeutic device for the delivering of the drug sodium diclofenac for uses as an anti-inflammatory is prepared by first pressing in a Manesty press an osmotic drug composition containing 75 mg of sodium diclofenac, 300 mg of sorbitol, 30 mg of sodium bicarbonate, 26 mg of pectin, 10 mg of polyvinyl pyrrolidone and 5 mg of stearic acid and pressing the composition in a cavity to a solid layer. Next, the cavity is charged with a second and greater force generating composition comprising 122 mg of pectin having a molecular weight of 90,000 to 130,000, 32 mg of mannitol, 20 mg of polyvinyl pyrrolidone and 2 mg of magnesium stearate and pressed to form a second layer in contacting relation with the first layer. The second layer had a density of 1.28 g/cm^3 and a hardness score of greater than 12 kg. Next, the two layer core is surrounded with a semi-permeable wall comprising 85 g of cellulose acetate having an acetyl content of 39.8%, and 15 g of polyethylene glycol 4000, 3 wt/wt % solid in a wall forming solvent comprising 1960 ml of methylene chloride and 819 ml of methanol. The coated device is dried for 72 hours at 50°C, and then a 0.26 mm diameter passageway is laser-drilled through the wall. The semi-permeable wall is 0.1 mm thick, the device has an area of 3.3 cm^2, and it has an average rate of drug release of 5.6 mg per hour over a 12 hour period. The cumulative amount released is illustrated in Figure 10. The small vertical bars represent the minimum and maximum drug release for five systems measured at that time.

EXAMPLE 5A

The procedure of Example 5 is followed for providing an osmotic device wherein the compartment contained a blend of osmopolymers. The compartment contained a first composition weighing 312 mg and consists of 48% sodium diclofenac drug, 38% poly(ethylene oxide) osmopolymer having a molecular weight of 200,000, 10% poly(ethylene glycol) osmopolymer having a molecular weight of 20,000, 2% sodium chloride, and 2% sodium chloride, and 2% magnesium stearate; and a second composition weighing 150 mg and consisting of 93% poly(ethylene oxide) having a molecular weight of 5,000,000, 5% sodium chloride, and 2% magnesium stearate.

EXAMPLE 6

In this example, the increase in osmotic pressure for a number of compositions comprising an osmagent and as osmopolymer are made for demonstrating the operative advantage provided by the invention. The measurements are made by measuring the amount of water imbibed across the semi-permeable wall of a bag containing as osmagent, or an osmopolymer, or a composition comprising an osmagent and an osmopolymer. The semi-permeable wall of the bag is formed of cellulose acetate having an acetyl content of 39.8%. The measurements are made by weighing the dry ingredients of the semi-permeable bag, followed by weighting the blotted semi-permeable bag, after the bag is in a water bath at 37°C for various lengths of time. The increase in weight is due to water imbibition across the semi-permeable wall caused by the osmotic pressure gradient across the wall. The osmotic pressure curves are illustrated in Figure 11. In Figure 11, the curved line with the triangles represents the osmotic pressure for poly(ethylene) oxide having a molecular weight of 5,000,000; the curved line with the circles represents the osmotic pressure for a composition comprising poly(ethylene) oxide having a molecular weight of 5,000,000 and sodium chloride with the ingredients present in the composition in the ratio of 9.5 parts osmopolymer to 0.5 parts osmagent; the curved line with squares represents a composition comprising the same osmopolymer and osmagent in the ratio of 9 parts osmopolymer to one part osmagent; the curved lines with hexagon represents the same composition comprising the osmopolymer and osmagent in the ratio of 8 parts to 2 parts; and the dashed lines represents the osmagent sodium chloride. The mathematical calculations are made using the formula $dw/dt=A(K\Delta\pi)/h$, wherein dw/dt is the rate of water imbibition over time, A is the area of the semi-permeable wall, and K is the permeability coefficient. Also, in Figure 11, W_H/W_p is the amount of water imbibed divided by the weight of osmopolymer plus osmagent.

EXAMPLE 7

An osmotic therapeutic device for dispensing sodium diclofenac is prepared by screening through a 40 mesh screen a composition comprising 49% of sodium diclofenac, 44% poly(ethylene) oxide having a molecular weight of 100,00, 2% sodium chloride and 3% hydroxypropylmethylcellulose, and then blending the screened composition with an alcohol solvent used in the ratio of 75 ml of solvent to 100 g of granulation. The wet granulation is screened through a 16 mesh screen, dried at room temperature for 48 hours under vacuum, passed through a 16 mesh screen and blended with 2% 80 mesh screened magnesium stearate. The composition is compressed as described above.

Next, a composition comprising 73.9% of pectin, having a molecular weight of 90,000 to 130,000, 5.8% microcrystalline cellulose, 5.8% polyvinyl pyrrolidone, 14.3% sodium chloride and 2% sucrose is passed through a 40 mesh screen, blended with an organic solvent in the ratio of 100 ml of solvent to 100 g of granulation for 25 minutes, passed through a 16 mesh screen, dried for 48 hours at room temperature under vacuum, again passed through a 16 mesh screen, blended with 2% magnesium stearate, and then compressed onto the compressed layer described in the above paragraph. The dual layered drug core is coated by dipping in a wall forming composition comprising

80% cellulose acetate having an acetyl content of 39.8%, 10% polyethylene glycol 4000, and 10% hydroxypropylmethylcellulose. A passageway is drilled through the wall communicating with the drug containing composition. The passageway diameter is 0.38 mm. The theoretical cumulative release profile for the device is depicted in Figure 12. Figure 13 depicts the theoretical release rate in mg per hour for the osmotic device.

EXAMPLE 8

The procedure of Example 7 is repeated with all conditions as described except that the osmopolymer in the drug composition is polyoxyethylene polyoxypropyleneblock copolymer having a molecular weight of about 12,500.

EXAMPLE 9

An osmotic device is made by following the above procedures. The device of this example comprises a single composition comprising 50% of sodium diclofenac, 46% of poly(ethylene) oxide having a molecular weight of 100,000, 2% sodium chloride and 2% magnesium stearate. The device has a semi-permeable wall comprising 90% cellulose acetate comprising 39.8% acetyl, and 10% polyethylene glycol 4000. The cumulative amount released for this device comprising the single composition is 40% of the device comprising two compositions. The cumulative amount released is illustrated in Figure 14.

EXAMPLE 10

The *in vivo* and *in vitro* mean cumulative releases of diclofenac sodium from an osmotic device comprising a first osmotic composition comprising 75 mg of diclofenac sodium 67 mg of poly(ethylene) oxide having a molecular weight of 100,000, 3.0 mg of sodium chloride, 4.5 mg of hydroxypropylmethylcellulose and 3.0 mg of magnesium stearate; a second osmotic composition distant from the releasing passageway comprising 51 mg of poly(ethylene) oxide having a molecular weight of 5,000,000, 22.5 mg of sodium chloride and 1.5 mg of magnesium stearate; and, surrounded by a semi-permeable wall comprising 90% cellulose acetate having an acetyl content of 39.8% and 10% polyethylene glycol 4000 was measured in vivo and in vitro in laboratory dogs. The amounts of drug released at various times in vivo were determined by administering a series of devices to the animal and measuring the amount released from the corresponding device at the appropriate residence time. The results are depicted in Figure 15, wherein the circles with the bars are the in vitro mean cumulative releases and the triangles with the bars are the in vivo mean cumulative releases.

The in vivo and in vitro mean cumulative release for a device containing nifedipine was measured as described immediately above. The osmotic device comprised a composition adjacent to the passageway comprising 30 mg of nifedipine, 106.5 mg of poly(ethylene) oxide having a molecular weight of 200,000, 3 mg of potassium chloride, 7.5 mg of hydroxypropylmethylcellulose and 3 mg of magnesium stearate; a composition distant form the passageway comprising 52 mg of poly(ethylene) oxide having a molecular weight of 5,000,000, 22 mg of sodium chloride and 1.5 mg of magnesium stearate; and a semi-permeable wall comprising 95% cellulose acetate having an acetyl content of 39.8% and 5% hydroxypropylmethylcellulose. Figure 16 depicts the release from the system. In Figure 16 the circles represent the in vivo cumulative release and the triangles represent the in vitro means cumulative release.

EXAMPLE 11

The procedure of Example 10 is followed for making an osmotic therapeutic delivery system comprising: a first or drug composition weighing 638 mg and consisting 96% cephalexin hydrochloride, 2% Poviclone (polyvinyl pyrrolidone) and 2% magnesium stearate; a second, or osmotic deriving composition weighing 200 mg and consisting of 68.5% poly(ethylene oxide) having a molecular weight of 5×10^6, 29.5% sodium chloride, and 2% magnesium stearate; a semi-permeable wall weighing 55.8 mg consisting of 80% cellulose acetate having an acetyl content of 39.8%, 14% polyethylene glycol 4000, and 14% hydroxypropylmethylcellulose; and an osmotic orifice having a diameter of 0.039 mm. The device has an average rate of release of about 54 mg per hour over a period of 9 hours.

The novel osmotic system of this invention uses dual means for the attainment of precise release rate of drugs that are difficult to deliver in the environment of use, while simultaneously maintaining the integrity and the character of the system. While there has been described and pointed out features and advantages of the invention as applied to the presently preferred embodiments, those skilled in the dispensing art will appreciate that various modifications, changes, additions and omissions in the system illustrated and described can be made without departing from the spirit of the invention.

CLAIMS

1. A device for the delivery at a controlled rate a beneficial agent to an environment of use, the device comprising:

a). a wall formed in at least a part of a composition permeable to the passage of an exterior fluid present in the environment of use, the wall surrounding and forming;

b). a compartment;

c). a first composition in the compartment, said first composition comprising a beneficial agent, an osmagent and an osmopolymer;

d). a second composition in the compartment, said second composition comprising an osmagent and an osmopolymer; and

e). a passageway in the wall communicating with the first composition and the exterior of the device for delivering the beneficial agent from the device.

2. The device for the delivery at a controlled rate the beneficial agent according to claim 1, wherein the wall forming composition comprises a member selected from the group consisting of cellulose acylate, cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose diacetate, cellulose triacetate, ethyl cellulose, cellulose acetate butyrate, cellulose acetate propionate, hydroxypropylmethylcellulose, hydroxyloweralkylcellulose, methylcellulose, methylethylcellulose and mixtures thereof.

3. The device for the delivery at a controlled rate the beneficial agent according to claim 1, wherein the first composition is in the compartment as a layer, and the second composition is in the compartment as a layer.

4. The device for the delivery at a controlled rate the beneficial agent according to claim 1, wherein the first composition imbibes external fluid through the wall into the compartment, and the second composition imbibes external fluid through the wall into the compartment.

5. The device for the delivery at a controlled rate the beneficial agent according to claim 1, wherein the osmopolymer comprising the second composition has a molecular weight greater than the molecular weight of the osmopolymer comprising the first composition.

6. The device for the delivery at a controlled rate the beneficial agent according to claim 1, wherein the beneficial agent is a drug.

7. The device for the controlled delivery of the beneficial agent to the environment of use according to claim 1, wherein the wall is a laminate comprising a semi-permeable lamina and a microporous lamina.

8. The device for the controlled delivery of the beneficial agent to the environment of use according to claim 1, wherein the composition forming the wall contains polyethylene glycol.

9. The device for the controlled delivery of the beneficial agent to the environment of use according to claim 1, wherein the osmopolymer in the first composition is poly(ethylene oxide).

10. The device for the controlled delivery of the beneficial agent to the environment of use according to claim 1, wherein the osmopolymer in the second composition is poly(ethylene oxide).

11. The device for the controlled delivery of the beneficial agent to the environment of use according to claim 1, wherein the agent is the drug nifedipine, verapamel, diltiazen, diclofenae, propanolol, proszin, ibuprofen, ketoprofen, haloperiodol, indomethacin, and cephalexin.

12. A device as claimed in claim 1 and substantially as herein described and/or with reference to the accompanying drawings.

13. Each and every novel embodiment herein set forth either separately or in combination.

New claims or amendments to claims filed on 3.7.84
Superseded claims 1—13
New or amended claims:—

1. A device for the delivery at a controlled rate a beneficial agent to an environment of use, the device comprising:

a) a wall formed in at least a part of a composition permeable to the passage of an exterior fluid present in the environment of use, the wall surrounding and forming;

b) a compartment;

c) a first composition in the compartment, said first composition comprising a beneficial agent and an osmopolymer;

d) a second composition in the compartment, said second composition comprising an osmagent and an osmopolymer; and

e) a passageway in the wall communicating with the first composition and the exterior of the device for delivering the beneficial agent from the device.

2. The device for the delivery at a controlled rate the beneficial agent according to claim 2, wherein the wall forming composition comprises a member selected from the group consisting of cellulose acylate, cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose diacetate, cellulose triacetate, ethyl cellulose, cellulose acetate butyrate, cellulose acetate propionate, hydroxypropylmethylcellulose, hydroxyloweralkylcellulose, methylcellulose, methylethylcellulose and mixtures thereof.

3. The device for the delivery at a controlled rate the beneficial agent according to either of claims 1 or 2, wherein the first composition is in the compartment as a layer, and the second composition is in the compartment as a layer.

4. The device for the delivery at a controlled rate the beneficial agent according to any preceding claim, wherein the first composition imbibes external fluid through the wall into the compartment, and the second composition imbibes external fluid through the wall into the compartment.

5. The device for the delivery at a controlled rate the beneficial agent according to any preceding claim, wherein the osmopolymer comprising the second composition has a molecular weight greater than the molecular weight of the osmopolymer comprising the first composition.

6. The device for the delivery at a controlled rate the beneficial agent according to any preceding claim, wherein the beneficial agent is a drug.

7. The device for the controlled delivery of the beneficial agent to the environment of use according to any preceding claim, wherein the wall is a laminate comprising a semi-permeable lamina and a microporous lamina.

8. The device for the controlled delivery of the beneficial agent to the environment of use according to any preceding claim, wherein the composition forming the wall contains polyethylene glycol.

9. The device for the controlled delivery of the beneficial agent to the environment of use according to any preceding claim, wherein the osmopolymer in the first composition is poly(ethylene oxide).

10. The device for the controlled delivery of the beneficial agent to the environment of use according to any preceding claim, wherein the osmopolymer in the second composition is poly(ethylene oxide).

11. The device for the controlled delivery of the beneficial agent to the environment of use according to any preceding claim, wherein the agent is the drug nifedipine, verapamel, diltiazen, diclofenae, propanolol, proszin, ibuprofen, ketoprofen, haloperiodol, indomethacin, and cephalexin.

12. The device for the controlled delivery of the beneficial agent to the environment of use according to any preceding claim, wherein the first composition comprises an osmagent.

13. A device as claimed in claim 1 and substantially as herein described and/or with reference to the accompanying drawings.

14. Each and every novel embodiment herein set forth either separately or in combination.

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